

Mecamylamine Increases Nicotine Preference and Attenuates Nicotine Discrimination



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ROSE, J. E., A. SAMPSON, E. D. LEVIN AND J. E. HENNINGFIELD. *Mecamylamine increases nicotine preference and attenuates nicotine discrimination*. PHARMACOL BIOCHEM BEHAV 32(4) 933-938, 1989.—Eight subjects evaluated various qualities of cigarette smoke after being given a range of doses (0, 2.5, 10 and 20 mg) of the nicotinic receptor blocker mecamylamine. In one test condition, subjects were given either high or low nicotine tobacco smoke to determine the effects of mecamylamine on their subjective responses. In another test condition, subjects were allowed to adjust the nicotine dose level of the smoke to determine the effects of mecamylamine on dose preference. When the subjects evaluated puffs of smoke with high and low nicotine content, mecamylamine caused a dose-related decrease in the self-rated strength and harshness of the high nicotine dose level smoke. In contrast, there was little effect on the low dose smoke. At the highest mecamylamine dose (20 mg) there was no significant difference in the ratings of high and low nicotine cigarettes. Low doses of mecamylamine decreased the reported desire for a cigarette, and also attenuated the reduction in desire for a cigarette caused by smoking. When the subjects were allowed to select their preferred level of nicotine intake using a smoke mixing device, the 10 and 20 mg doses of mecamylamine caused a significant increase in self-administered nicotine dose level. Despite this compensatory increase in nicotine self-administration, the reduction in desire for a cigarette after smoking was still less than after placebo.

Smoking Mecamylamine Nicotine Satisfaction Preference Antagonist Reinforcement Tobacco

MECAMYLAMINE, a nicotinic receptor blocker, has provided a useful tool for studying the role of nicotine in cigarette smoking. By selectively blocking the pharmacologic effects of nicotine, while leaving the nonnicotinic effects of tobacco intact, mecamylamine can be used to examine the role of nicotine in smoking. Previous studies have shown that mecamylamine increases tobacco smoke self-administration (2, 3, 7, 8, 15). The common conclusion of these studies has been that smokers increase their cigarette intake in an attempt to overcome the blockade of central nicotinic stimulation imposed by mecamylamine. However, the relationship of tobacco smoke self-administration to the reinforcing effects of nicotine is not well understood.

In the present study, we measured the effects of mecamylamine on the specific desire for nicotine, using a recently developed method of measuring smokers' nicotine preference. With this method, the subjects manipulate a smoke mixing device to control the proportion of smoke obtained from cigarettes of high and a low nicotine delivery, but of equal tar delivery (4). By turning a knob, subjects can control the amount of nicotine in each puff without altering puffing topography or nonnicotine constituents in smoke.

We have found this smoke mixing technique to be sensitive to shifts in nicotine preference induced by periods of cigarette deprivation, which raises nicotine preference, or by transdermal administration of nicotine, which lowers nicotine preference (10,12). Our hypothesis was that mecamylamine would increase nicotine preference.

Because inhaled nicotine produces both peripheral sensory actions in the mouth and upper respiratory tract, as well as actions in the autonomic ganglia and central nervous system, any combination of these effects could conceivably determine nicotine discriminations and nicotine self-administration. Inasmuch as relatively little is known about the specific cues that human subjects use to discriminate between puffs of different nicotine content, we assessed the effects of mecamylamine on their sensory evaluation of a programmed series of high and low nicotine puffs. If the peripheral effects of nicotine were important, then mecamylamine would attenuate the ratings of high nicotine smoke.

In addition to measuring the effects of mecamylamine on smokers' discrimination and intake of nicotine, we were also interested in subjects' reports regarding the enjoyment of smoking

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TABLE 1
EXPERIMENTAL TIMELINE

Time After Mecamylamine (min)	Event
-10	Preliminary nicotine preference test*
0	Mecamylamine or placebo administration
50	First postdrug nicotine preference test*
110	Second postdrug nicotine preference test*
160	Nicotine discrimination test (series of 10 low nicotine puffs and 10 moderate nicotine puffs)
170	Third postdrug nicotine preference test*

*Nicotine preference tests presented high, medium and low nicotine puffs followed by 10 min of *ad lib* smoking, using smoke-mixing device to adjust nicotine delivery as desired.

and desire for a cigarette. Conceivably, mecamylamine might induce a sufficient compensatory increase in nicotine preference to maintain both the enjoyment of smoking and the ability of smoking to suppress the subsequent desire for a cigarette. Obtaining data pertaining to subjective responses along with data on nicotine dose preference may enhance our understanding of the specific determinants of nicotine self-administration in human cigarette smokers.

METHOD

Subjects

Eight male smokers aged 21–50, who smoked at least 30 cigarettes per day (nonmentholated, with at least 0.7 mg nicotine delivery by the FTC method), were recruited from a subject pool maintained by an independent agency under contract to the Addiction Research Center, Baltimore, MD.

Procedure

Subjects came to the laboratory (nonabstinent from smoking) on five mornings, which included a familiarization session followed by four mecamylamine dose conditions: 0 (placebo), 2.5 mg, 10 mg, and 20 mg given in a counterbalanced order. An outline of the timetable of each session is shown in Table 1.

Each session began with a preliminary nicotine preference measurement. Subjects were presented with puffs from a smoke mixing device that blended smoke from a high and a low nicotine cigarette. The cigarettes, a commercial brand (Marlboro Lights 100s), were modified by injecting either nicotine (6 mg in a 30% aqueous solution) or water into the filter to vary the nicotine delivery selectively. In a previous study (4) we found that tar delivery (10.6 mg) is unaffected by this technique and that the high and low nicotine cigarettes delivered (by standard FTC smoking procedures) approximately 1.5 and 0.75 mg nicotine, respectively. To assess the subjects' preferred nicotine delivery, they were first asked to take one puff each from the low, middle and high nicotine settings of the smoke mixer. Subsequently, they continued smoking *ad lib* for ten minutes, adjusting the mixer setting as desired. Subjects rated each puff for strength, harshness and desirability, using a ten-point rating scale (0–9). The mixer dial setting selected was recorded before each puff to allow calculation of the proportion of smoke obtained from the high nicotine cigarette. The side of the mixer containing the high nicotine cigarette was counterbalanced across subjects, but remained consistent for a given

subject on different days.

After a preliminary nicotine preference test, a capsule was administered (double-blind) containing a dose of mecamylamine or placebo. The sequence of doses was counterbalanced across subjects using Latin squares. Subjects received three additional nicotine preference assessments at 50-minute intervals, during which it was expected that the mecamylamine would be absorbed.

To examine the influence of mecamylamine on nicotine discrimination, a set of 20 puffs was presented immediately before the fourth (and final) nicotine preference test. Ten of these puffs were of low nicotine delivery (from the 0.75 mg nicotine cigarette with water injected into the filter) and ten randomly interspersed puffs were of moderate nicotine delivery (4 mg nicotine injected into the cigarette filter—estimated nicotine delivery of 1.2 mg). Puffs were presented every 30 seconds and the random sequences of low and moderate nicotine puffs were varied for each subject. Subjects rated each of these puffs for strength, harshness and desirability. Puff duration was also measured by presenting these puffs through a cigarette holder attached to a pressure transducer. Subjects also reported their desire for a cigarette before and after the nicotine discrimination test and each nicotine preference test, using a ten-point scale. At these times expired air carbon monoxide concentrations and skin temperature were measured, and standing and supine heart rate and blood pressure were recorded. To monitor possible side effects of mecamylamine, subjects completed a checklist which included the following items: visual disturbances, dry mouth, chills, constipation, urinary difficulty, dizziness, fainting, and drug effect.

For each measure the data were assessed by a repeated measures analysis of variance. Mecamylamine dose and nicotine level were factors with all of the measures. In addition, time of testing was a factor in the analysis of measures taken repeatedly. Analyses for linear and quadratic trends for increasing nicotine and mecamylamine doses were also conducted. When significant interactions occurred, tests of the simple main effects of mecamylamine or nicotine were performed.

RESULTS

The main findings of the study were that mecamylamine pretreatment produced dose-related decreases in the subjective effects of smoking—ratings of puff strength and harshness, and reduction in desire for a cigarette after smoking—whereas the preferred self-administered nicotine dose level was increased.

Nicotine Discriminability During Nicotine Preference Tests

The discriminability in strength and harshness between the high, medium and low nicotine puffs at the beginning of each nicotine preference test were significantly reduced by mecamylamine. There were no significant effects of time of testing; therefore, Fig. 1a and b show the average ratings for the tests one and two hours after mecamylamine administration. As shown in Fig. 1a, the self-rated strength of the medium and high nicotine puffs was markedly reduced by mecamylamine, while the low nicotine puffs were relatively unaffected. There were significant main effects of mecamylamine, $F(2,14)=7.68$, $p<0.001$, and nicotine, $F(2,14)=9.59$, $p<0.01$, both characterized by significant linear trends ($p<0.025$); mecamylamine decreased the perceived strength and nicotine increased strength. Interestingly, there was a significant mecamylamine \times nicotine interaction, $F(6,42)=2.76$, $p<0.025$. Mecamylamine significantly decreased the discriminability of the nicotine content of the smoke. It had relatively greater effects in reducing the perception of higher nicotine smoke. Mecamylamine significantly reduced the per-

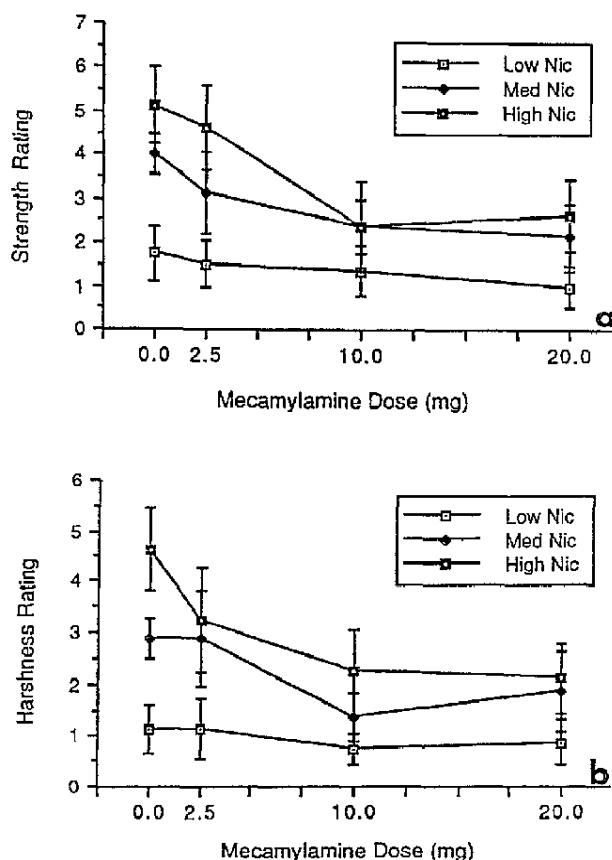


FIG. 1. (a) Self-rated strength of low, medium and high nicotine cigarettes: average of sessions one and two hours before mecamylamine administration (mean \pm standard error of the mean). (b) Self-rated harshness of low, medium and high nicotine cigarettes: average of sessions one and two hours after mecamylamine administration (mean \pm standard error of the mean).

ceived strength of high ($p < 0.001$) and medium ($p < 0.05$) level nicotine smoke, while there were no significant effects with low nicotine smoke.

Similar effects were detected with harshness. As shown in Fig. 1b, the harshness of the medium and high nicotine puffs was markedly reduced by mecamylamine, while the low nicotine puffs were once again relatively unaffected. There were significant main effects of mecamylamine, $F(3,21)=6.00$, $p < 0.01$, and nicotine, $F(2,14)=7.58$, $p < 0.01$, characterized in both cases by significant linear trends ($p < 0.025$), with mecamylamine decreasing harshness and nicotine increasing it. As with strength, there was a significant mecamylamine \times nicotine interaction, $F(6,42)=2.97$, $p < 0.025$, with mecamylamine decreasing the discriminability of the nicotine content of smoke. Mecamylamine significantly decreased ($p < 0.001$) the harshness of the high nicotine smoke, but did not have any significant effects on medium and low nicotine smoke.

There were no significant mecamylamine or nicotine or interactive effects on puff desirability during the first three puffs of the nicotine preference tests.

Nicotine Discrimination Test

Similar clear-cut effects of mecamylamine on tobacco smoke

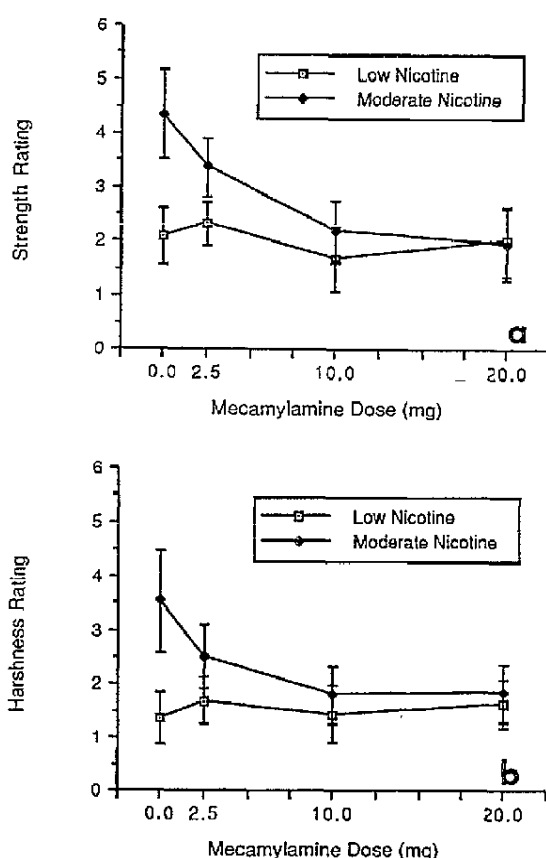


FIG. 2. (a) Self-rated strength of low and moderate nicotine cigarettes: average of sessions one and two hours after mecamylamine administration (mean \pm standard error of the mean). (b) Self-rated harshness of low and moderate nicotine cigarettes: average of sessions one and two hours after mecamylamine administration (mean \pm standard error of the mean).

ratings were also seen during the controlled series of twenty puffs of the nicotine discrimination test that preceded the final nicotine preference test. In the placebo condition the moderate nicotine cigarette was rated as stronger (Fig. 2a) and harsher (Fig. 2b) than the low nicotine cigarette. Mecamylamine caused a dose-related reduction in the rated strength and harshness of the moderate nicotine cigarette, while no effect was seen with the low nicotine cigarette. Significant mecamylamine \times nicotine interactions were seen for both strength, $F(3,21)=6.43$, $p < 0.005$, and harshness, $F(3,21)=4.09$, $p < 0.025$. Follow-up analyses of the simple main effects on strength ratings (ANOVA at each mecamylamine dose level) detected significant nicotine-related differences ($p < 0.05$) with 0, 2.5 and 10 mg doses of mecamylamine. With harshness ratings, significant simple main effects ($p < 0.05$) were detected with the 0 and 2.5 mg doses of mecamylamine. Thus, with both measures mecamylamine decreased the differences between the moderate and low nicotine cigarettes so that by the highest (20 mg) dose, no difference in strength or harshness was detected between these two types of cigarettes.

Despite the effects of mecamylamine on puff strength and harshness ratings, no significant effects were seen on puff desirability. Mecamylamine caused a significant, $F(3,21)=7.48$, $p < 0.001$, dose-related increase in puff duration. Since the me-

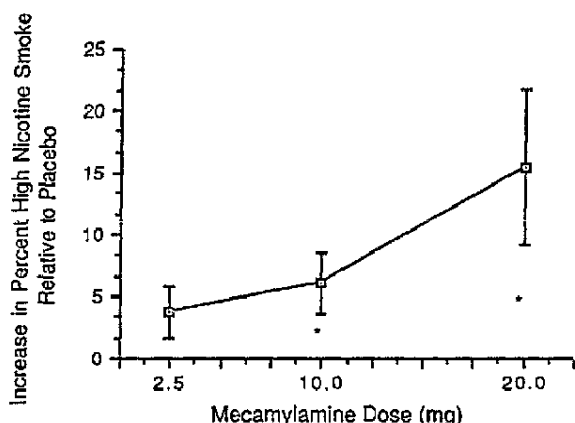


FIG. 3. Nicotine preference during the first 2 puffs of the smoke mixer test (mean \pm standard error of the mean). \star : $p < 0.05$.

dium and low nicotine puffs were randomly interspersed with no warning to the subject, no nicotine effect was expected and none was seen. Mean puff duration was 1.8 ± 0.2 (mean \pm SEM) sec in the placebo condition and rose to a high of 2.2 ± 0.2 sec in the 20 mg mecamylamine condition.

Nicotine Dose Preference

After initial test puffs at low, medium and high nicotine smoke levels, the subjects were allowed to select their preferred strength of tobacco smoke during each nicotine preference test. A previous study (4) suggested that the initial nicotine preference during the first two voluntary puffs would be the most sensitive index of subjects' nicotine preference. A mecamylamine Dose \times Time ANOVA was conducted for the four mecamylamine dose conditions and the first three hourly nicotine preference tests (omitting the last nicotine preference test that followed the nicotine discrimination test, which is discussed below). The overall analysis detected a significant Dose \times Time interaction, $F(6,42)=2.43$, $p < 0.05$, as mecamylamine increased nicotine preference over the first two hours after administration. There was no main effect of Time on nicotine preference. Follow-up analyses of the simple main effects of mecamylamine during the three different test periods detected a significant mecamylamine effect during the nicotine preference test two hours after administration, $F(3,21)=4.40$, $p < 0.025$. There was also a tendency for a mecamylamine-induced increase in nicotine preference during the nicotine preference test one hour after administration, but this was not significant. Individual comparisons of the drug doses vs. the placebo for the 2-hour postmecamylamine nicotine preference test showed that the 10 and 20 mg doses of mecamylamine significantly ($p < 0.05$) increased nicotine preference (Fig. 3). The 2.5 mg dose also showed a tendency towards an increase which was not significant. In a separate analysis, there was no effect of mecamylamine on nicotine preference during the final nicotine preference test.

There were no mecamylamine-induced differences in the number of puffs or individual puff desirability during the nicotine preference tests.

Desire to Smoke and Smoking Satisfaction

The self-rated desire for a cigarette prior to each nicotine

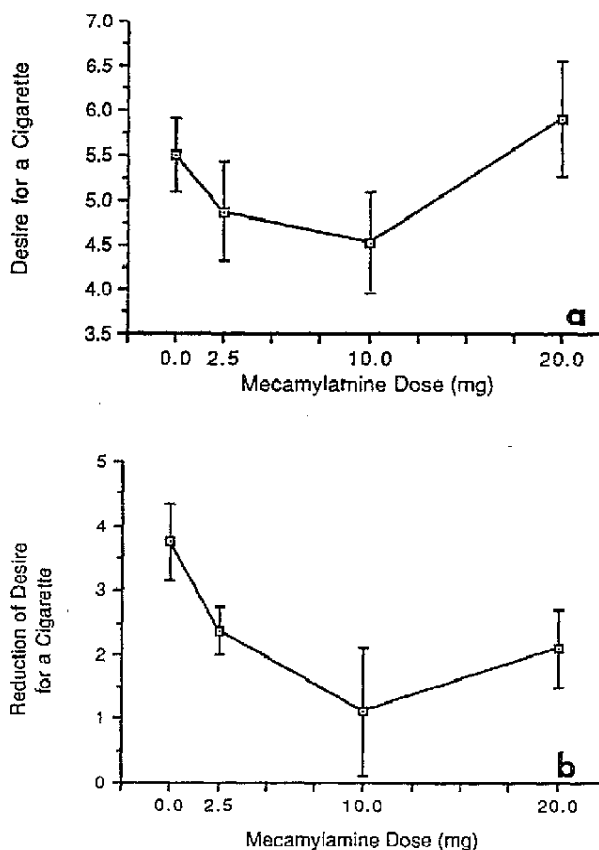


FIG. 4. (a) Self-rated desire for a cigarette (mean \pm standard error of the mean). (b) Smoking-induced reduction in desire for a cigarette, three hours after mecamylamine administration (mean \pm standard error of the mean).

preference test was significantly, $F(3,21)=3.53$, $p < 0.05$, affected by mecamylamine. This drug effect was characterized by a significant quadratic trend ($p < 0.05$) with low doses of mecamylamine reducing desire for a cigarette and higher doses increasing it (Fig. 4a).

Because all subjects took the same number of high and low nicotine puffs in the nicotine discrimination test (three hours after mecamylamine administration), an analysis was conducted on pre- vs. postsmoking desire for a cigarette. During this segment the smoking-induced reduction in desire for a cigarette showed a significant mecamylamine effect, $F(3,21)=3.22$, $p < 0.05$, characterized by a significant linear decrease, $F(1,7)=9.60$, $p < 0.025$, with increasing mecamylamine doses. There was an apparent upturn at the 20 mg dose (Fig. 4b), but the quadratic trend was not significant.

Physiological and Self-Report Data

None of the somatic measures taken were affected by mecamylamine; nor were there any significant self-ratings or observer ratings of a drug effect. Standing and supine heart rates were slightly, though nonsignificantly increased by mecamylamine.

Standing and supine systolic and diastolic blood pressure showed slight though nonsignificant decreases with mecamlamine.

Changes in carbon monoxide (CO) levels were affected by mecamlamine. CO (ppm) in expired air rose in all treatment conditions over the course of a session. This rise was enhanced by all of the mecamlamine treatments, but no linear dose effect relationship was seen. There was, however, a significant quadratic trend ($p < 0.025$), with the lower doses enhancing the rise in CO more than the high dose. With the placebo the rise in CO over the course of the session was 14.5 ± 2.8 ppm, while in the mecamlamine sessions it was 19.4 ± 2.6 ppm with 2.5 mg, 19.0 ± 2.6 ppm with 10 mg and 16.6 ± 2.7 with 20 mg.

DISCUSSION

Results from the present study demonstrated a profound influence of mecamlamine on smoking behavior and subjective ratings of cigarette smoke. Mecamlamine decreased the perceived strength and harshness of cigarette smoke and reduced the effect of smoking on subsequent desire for a cigarette. Mecamlamine also increased CO levels, average puff duration and preferred nicotine concentration of cigarette smoke. Although plasma nicotine levels were not measured, these behavioral findings suggest that the subjects self-administered a higher dose of nicotine in an attempt to overcome the blockade of nicotinic receptors by mecamlamine. The relative absence of adverse side effects after treatment with mecamlamine suggests that these changes in smoking behavior were probably not due to a feeling of malaise induced by mecamlamine, but were specific to a decreased action of nicotine. The side effects of mecamlamine may have been greater if the procedure had required prolonged smoking abstinence, as the repeated smoking in the present study could have offset the side effects of mecamlamine.

The mecamlamine-related decrease in the effect of smoking on subsequent desire for a cigarette may have been due in part to the blockade of central nicotinic receptors but probably was also partly due to peripheral nicotinic blockade. A role for peripheral sensory effects of nicotine in reducing desire for a cigarette was suggested by the effects of mecamlamine on ratings of puff harshness. While strength could refer both to peripheral and central effects, the striking reduction in the rated harshness of nicotine in smoke clearly implies a reduction in sensitivity to peripheral sensory stimulation. This finding supports a growing body of research which suggests that peripheral sensory effects of smoke, which are mediated in part by nicotine, contribute to smoking satisfaction (1, 9, 11, 13, 14). Lundberg (6) showed in rats that the irritant response to cigarette smoke could be blunted by hexamethonium, a peripherally acting nicotinic receptor antagonist. Thus, the blockade of the sensory cues of nicotine by mecamlamine may have partially accounted for the effect we observed on reduction in desire for a cigarette. Further studies investigating the effects of selective peripheral nicotinic blockade on desire for a cigarette and smoking satisfaction should clarify the role of peripheral nicotinic stimulation in smoking behavior.

The time course of mecamlamine's effects could have been influenced by a number of unique features of our procedure. The repeated self-dosing with nicotine could have produced varying nicotine levels that interacted with mecamlamine over the course of a session; additionally, subjects may have learned throughout nicotine preference tests within a session that the effects of smoking were blunted by mecamlamine. Additional practice and habituation effects could have interacted in unknown ways with the dependent measures. However, the overall conclusion remains that mecamlamine's peripheral and/or central blockade of nico-

tine led to the increases in nicotine preference and decreases in discriminability of nicotine we observed.

Nonnicotinic aspects of cigarette smoke that contribute to ratings of strength and harshness were also suggested. In contrast to the potent dose-related effect of mecamlamine in decreasing the rated strength and harshness of high nicotine puffs, it had little or no effect in decreasing the strength and harshness of medium and low nicotine puffs. The rated differences between these types of puffs was eliminated by the 20 mg dose of mecamlamine. Nonnicotinic sensory aspects of cigarette smoke such as sight, scent and flavor may have been responsible for the residual ratings of strength and harshness after the high dose of mecamlamine. However, since the strength and harshness ratings of the low nicotine smoke was quite low with the placebo, the lack of effect of mecamlamine may have been due to a floor effect of the rating scale. The nonnicotine components of cigarette smoke may have affected the results in another important way. The ratio of nicotine to tar in mainstream cigarette smoke is a critical determinant of strength and harshness of cigarette smoke (4). Hence, strength and harshness probably increased more dramatically with increasing nicotine delivery in the nicotine injection procedure we used than if the high nicotine puffs increased tar delivery proportionately. As a result, the effect of mecamlamine on the discrimination of strength and harshness of nicotine may have been especially pronounced.

The decrease in subjective effects of nicotine caused by low doses of mecamlamine in this study replicates an earlier finding (3). Originally, this decrease in response to nicotine was thought to be potentially useful in promoting smoking cessation. By blocking the reinforcing effects of smoking, mecamlamine could potentially encourage smoking cessation and decrease the tendency to relapse. However, the finding that mecamlamine also causes an increase in desire for a cigarette and an increase in smoking behavior, has attenuated interest in the possible use of mecamlamine in smoking cessation. In the present study, we found compensatory smoking with the 20 mg dose of mecamlamine. In contrast, doses of 2.5 and 10 mg did not increase nicotine preference, while they were effective in decreasing one of the subjective effects sought from smoking—a reduction in the desire for a cigarette after smoking. However, the lowest dose of mecamlamine did have the effect of increasing CO levels, suggesting that there may have been some compensatory increase in smoke inhalation. Nonetheless, the low doses (2.5 and 10 mg) did not increase, and possibly decreased, the desire for a cigarette prior to smoking (see Fig. 4a). These results indicate that nicotine blockade is not necessarily accompanied by an increased desire for cigarettes. Desire for cigarettes may be induced by at least two processes: the positive rewarding properties of smoking and the negative feelings of withdrawal. Low doses of mecamlamine may reduce the positive reinforcing effects of smoking without inducing substantial withdrawal, thus decreasing the desire to smoke. In contrast, at higher doses of mecamlamine, feelings of withdrawal may be more pronounced and result in an increased desire for a cigarette. The effects of low doses of mecamlamine suggest that the use of nicotinic antagonists as treatments for nicotine dependence warrants further exploration (5,16). Controlled studies of chronic mecamlamine administration need to be conducted to assess the clinical potential of mecamlamine in smoking cessation treatment.

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